Electrophysiological Effects of Late Percutaneous Coronary Intervention for Infarct-Related Coronary Artery Occlusion

The Occluded Artery Trial–Electrophysiological Mechanisms (OAT-EP)

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Background—The Occluded Artery Trial–Electrophysiological Mechanisms (OAT-EP) tested the hypothesis that opening a persistently occluded infarct-related artery by percutaneous coronary intervention and stenting (PCI) after the acute phase of myocardial infarction compared with optimal medical therapy alone reduces markers of vulnerability to ventricular arrhythmias.

Methods and Results—Between April 2003 and December 2005, 300 patients with an occluded native infarct-related artery 3 to 28 days (median, 12 days) after myocardial infarction were randomized to PCI or optimal medical therapy. Ten-minute digital Holter recordings were obtained before randomization, at 30 days, and at 1 year. The primary end point was the change in $\alpha_1$, a nonlinear heart rate variability parameter, between baseline and 1 year. Major secondary end points were the changes in the filtered QRS duration on the signal-averaged ECG and variability in T-wave morphology (T-wave variability) between baseline and 1 year. There were no significant differences in the changes in $\alpha_1$ ($-0.04$; 95% CI, $-0.12$ to $-0.04$), filtered QRS (2.2 ms; 95% CI, $-1.4$ to $-5.9$ ms), or T-wave variability (3.0 $\mu$V; 95% CI, $-4.8$ to 10.7 $\mu$V) between the PCI and medical therapy groups (medical therapy change minus PCI change). Multivariable analysis revealed that the results were unchanged after adjustment for baseline clinical variables and medication treatments during the Holter recordings.

Conclusions—PCI with stenting of a persistently occluded infarct-related artery during the subacute phase after myocardial infarction compared with medical therapy alone had no significant effect on changes in heart rate variability, the time-domain signal-averaged ECG, or T-wave variability during the first year after myocardial infarction. These findings are consistent with the lack of clinical benefit, including no reduction in sudden death, with PCI for stable patients with persistently occluded infarct-related arteries after myocardial infarction in the main OAT. (Circulation. 2009;119:779-787.)

Key Words: arrhythmia • death, sudden • electrocardiography • myocardial infarction • stents

Early coronary reperfusion with either thrombolytics or primary percutaneous coronary intervention (PCI) reduces long-term mortality in patients who present with ST-segment elevation myocardial infarction (MI).1 Early coronary reperfusion has been correlated with increased heart rate variability (HRV) and a decreased incidence of late potentials, suggesting that at least part of the clinical benefit of early reperfusion is explained by a decreased vulnerability to ventricular arrhythmias.2,3 However, up to one third of eligible patients do not receive effective early reperfusion because of such factors as late presentation or lack of efficacy of thrombolytics.3,4

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The late open artery hypothesis posits that clinical outcomes can be improved by late opening of persistently occluded infarct-related arteries (IRAs) during the subacute phase of MI, when myocardial salvage is not anticipated.5 Several mechanisms have been proposed to account for the
putative benefit of late reperfusion, including stabilization of the electrophysiological substrate and downstream prevention of malignant ventricular arrhythmias. Although experimental studies have suggested that late reperfusion decreases arrhythmic events, clinical studies that have examined this question have been limited by small sample size, lack of treatment randomization, and technical factors such as lack of stenting that limited sustained vessel patency after PCI.7,8

The Occluded Artery Trial (OAT) was an international randomized trial funded by the National Heart, Lung, and Blood Institute that tested the hypothesis that PCI and stenting of occluded IRAs identified on days 3 to 28 after MI compared with medical therapy alone would reduce the combined incidence of death, recurrent MI, and New York Heart Association (NYHA) class IV heart failure.9 The Occluded Artery Trial–Electrophysiological Mechanisms (OAT-EP), also funded by the National Heart, Lung, and Blood Institute, is a mechanistic ancillary study of OAT. The primary aim of OAT-EP was to test the hypothesis that PCI plus optimal medical therapy would result in a greater increase in HRV during the first year after MI than optimal medical therapy alone. Major secondary aims were to test the hypothesis that PCI would reduce dynamic changes in T-wave morphology (T-wave variability [TWV]) and filtered QRS duration (fQRS) on the signal-averaged ECG (SAECG) at 1 year after MI.

Methods

Study Design

OAT-EP enrolled participants between April 2003 and December 2005 at 36 of 216 OAT sites with separate Institutional Review Board approval from OAT (see the online Data Supplement for the list of participating centers). OAT-EP patients were OAT participants who provided additional informed consent. Randomization to PCI and stenting plus optimal medical therapy (PCI) or optimal medical therapy alone was done using the same randomization process as for other OAT participants.

Patient Sample

Eligibility criteria for OAT-EP mirror those of OAT.9 Patients had a documented MI and underwent cardiac catheterization within 3 to 28 days. Day 1 was the date of symptom onset; hence, the minimum interval between symptom onset and the qualifying cardiac catheterization study was 24 hours. Angiographic criteria included IRA occlusion judged suitable for stenting and at least 1 high-risk criterion: proximal coronary occlusion subtending at least 25% of the left ventricle and/or left ventricular ejection fraction <50%. IRA occlusion was defined as 100% stenosis with Thrombolysis in Myocardial Infarction grade 0 or 1 antegrade flow. Patients with clinical instability, left main or 3-vessel disease, or severe inducible ischemia were excluded. OAT-EP patients also were required to be in sinus rhythm so that HRV and TWV could be measured10,11 and to have a QRS duration <120 ms so that the time-domain SAECG could be performed.12

Study Procedures

OAT-EP participants gave informed consent for participation before OAT randomization to minimize selection bias for participation in the ancillary study. Patients assigned to PCI were to undergo the procedure within 24 hours of randomization whenever possible. Ten-minute digital Holter monitor recordings were performed before randomization, at 30 days, and at 1 year with a Burdick 92510 recorder (Spacelabs-Burdick, Deerfield, Wis.). The recordings were performed with Frank leads (X, Y, Z) at a sampling rate of 1000 Hz with the patient lying quietly in the supine position. The digital Holter data were stored on personal computer cards, which were shipped to the Holter Core Laboratory at the University of Maryland for downloading and analysis. The OAT-EP Core Laboratory personnel were blinded to the OAT treatment randomization (PCI versus optimal medical therapy). The Holter data were manually edited to eliminate ectopic beats and signal noise and then analyzed for the fractal scaling exponent (α1), time- and frequency-domain HRV parameters, time-domain SAECG, and TWV as previously described.10–15 The SAECGs were acquired in accordance with the published recommendations for recording conditions, lead placement, sampling rate, and signal filtering.16 The analysis of α1 and TWV was conducted at the University of Rochester. Recordings were excluded from HRV analysis if the prevalence of ectopic beats or noisy segments exceeded 25%, from SAECG analysis if the noise level was >1 μV, and from TWV analysis if the heart rate was unstable or if excessive ectopy or noise was present.10–12

Study End Points

The primary study end point was the change in α1 at 1 year. Major secondary end points were the changes in fQRS and TWV at 1 year. These study end points were chosen to fully characterize the effects of PCI of occluded IRAs on the major determinants of arrhythmia vulnerability: the autonomic nervous system (HRV), impulse conduc-

Statistical Analysis

An intention-to-treat principle was used for the primary treatment-related analyses. The primary end point (α1) was evaluated with α = 0.05 for a 2-sided t test comparing change in α1 from baseline to 1 year between the 2 treatment groups. As in the main OAT trial, a value of P ≤ 0.01 for secondary analyses was considered strong evidence of association. Changes in α1 were normally distributed and suitable for the t test. Changes in TWV and fQRS were not normally distributed and were winsorized and then analyzed with the t test. Winsorization is a method to control the variability introduced by extreme values. This method typically identifies the top and bottom 5% and reduces them to the next highest (or lowest) value. This method permits the use of procedures that require a normal distribution (ie, multiple regression) while controlling the influence of these extreme values.17

The planned sample size of 300 subjects was chosen to provide 80% power to detect a clinically relevant difference of 0.1 in the change in α1 from baseline to 1 year between the 2 treatment groups on the basis of data from prior studies that indicated that baseline levels of α1 would be 1.0 with a common SD of 0.2.15,16 Because this outcome is a measure of longitudinal change, the correlation between the measurements at baseline and 1 year must be taken into account. We assumed that the SD in the change in α1 would be between 0.28 (for a correlation [ρ] of 0) and 0.169 (for ρ = 0.65) and that the SD of α1 would be the same at baseline and 1 year. From these assumptions, the study would have ≥80% power to detect a difference in α1 of 0.14 units (ρ = 0) to 0.083 units (ρ = 0.65) between the PCI and medical therapy patients. This calculation assumed a crossover rate of 25% (PCI in medical therapy patients within 30 days of randomization and no attempt at PCI or failed PCI, which are biological crossovers, in the PCI-assigned patients) and a 15% loss to follow-up.
The analyses were repeated for time-domain and frequency-domain HRV variables and for other time-domain SAECG variables. A secondary analysis was conducted with unpaired t tests to determine whether the study results were affected by inclusion of additional patients who were excluded because of lack of complete baseline and follow-up information. Secondary analyses of the primary and major secondary end points also were performed after the exclusion of crossovers (as-treated analysis). Other secondary analyses assessed the changes in the primary and major secondary end points at 30 days. A sensitivity analysis was conducted because recurrent MI during the year between the Holter measurements could affect changes in arrhythmia marker values. For this analysis, patients with recurrent MI were excluded from the analysis of changes in $\alpha_1$, fQRS, and TWV between baseline and 1 year.

For multivariable models, we used stepwise linear regression with backward elimination, with a value of $P=0.05$ required for a variable to be retained in the model. Separate multivariable models were constructed for the change in each arrhythmia marker variable between baseline and 1 year. The prespecified variables tested in each stepwise model were treatment group (PCI versus medical therapy), age, sex, race (white versus nonwhite), prior MI, interval between qualifying MI and the Holter recording, baseline values of the arrhythmia marker variable, hypertension, diabetes, multivessel disease, collateral arteries, baseline left ventricular ejection fraction, left anterior descending coronary artery culprit, thrombolitics, ST elevation or new Q waves on ECG, $\beta$-blocker use at baseline and 1 year, and angiotensin-converting enzyme use at baseline and 1 year. Because the models of change in $\alpha_1$, fQRS, and TWV had normally distributed residuals that exhibited homoscedasticity, these measures were suitable for analysis with linear regression.

To ensure that OAT-EP patients are representative of patients in the community with occluded IRAs after MI, we compared the clinical characteristics of OAT-EP patients with 3 relevant patient populations: other randomized OAT patients who did not participate in OAT-EP, the OAT pretrial registry, and the concurrent OAT registry. The variables for these comparisons were age, sex, left ventricular ejection fraction $\leq 50\%$, and culprit IRA. We also compared long-term outcomes in OAT-EP and other OAT patients to ensure that lower-risk patients were not inadvertently selected to participate in OAT-EP. These outcomes included the primary OAT end point (death, nonfatal reinfarction, or NYHA class IV heart failure) and its individual components. Kaplan-Meier life table analysis was used to calculate estimated event rates, and the log-rank test was used to compare outcomes.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

The target sample of 300 patients was successfully enrolled in OAT-EP, representing 14% of the OAT study population of 2201 patients. There were an additional 157 patients enrolled in OAT but not OAT-EP at participating sites; although the precise reasons for exclusion were not tracked, these patients typically were excluded because they did not meet the additional OAT-EP inclusion criteria, refused to consent for OAT-EP, were randomized before the baseline Holter data could be acquired, or were judged to be unlikely to return for the follow-up 1-year Holter because of distance from the enrolling site.

The observed crossovers were 14 failed PCIs and 1 PCI not done in the PCI group (10%) and 4 PCIs within 30 days in the medical therapy group (2.6%). The loss to follow-up, with reasons for patient attrition, is shown in Figure 1.

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**Figure 1.** OAT-EP study flow. BL indicates baseline.
baseline and follow-up data for the primary end point (α1) were available at baseline and 1 year for 79% of the study cohort. Complete data for the major secondary end points (fQRS and TWV) were available at baseline and 1 year for 57% and 69% of patients, respectively. This sample size yielded 80% power to detect a change of 0.1 unit in α1, 99% power to detect a 10-ms change in fQRS, and 91% power to detect a 10-V change in TWV, each of which represents a clinically relevant change.11–15 More patients were excluded from TWV and fQRS analyses because of excessive signal noise on some recordings, which prohibited performance of these analyses. Data were available at 1 year for α1, fQRS, and TWV for 86%, 76%, and 80% of patients, respectively.

**Baseline Characteristics**

The baseline clinical and angiographic characteristics of the PCI and medical therapy groups were similar in most respects, except for a significant difference in the prevalence of diabetes (Tables 1 and 2). There was no significant difference in the time from the qualifying MI to the Holter recording when the PCI and medical therapy groups were compared (13.3±8.6 versus 13.0±7.8 days, respectively). OAT-EP patients were representative of the larger OAT study cohort with respect to most clinical and angiographic characteristics. However, OAT-EP patients had a lower incidence of prior MI, were more likely to be hypertensive, were less likely to have received thrombolytic therapy for the index MI, and had a greater prevalence of multivessel disease (Tables 1 and 2).

The patients with and without complete data available for the primary end point at baseline and 1 year had similar baseline demographic characteristics, except for median days between MI and randomization (14 versus 7 days, respectively).

There were no significant differences between OAT-EP patients and patients in the OAT concurrent registry with respect to age, sex, and identity of the IRA (data not shown). Patients in the OAT pretrial registry were slightly older than OAT-EP patients (62 versus 57 years), and the registry had fewer men (72% versus 79%); however, there were no significant differences in the identity of the IRA and left ventricular ejection fraction (data not shown). There were no significant differences in the 3-year OAT primary end-point event rate (death, nonfatal reinfarction, or NYHA class IV heart failure) or its individual components when OAT-EP and other OAT patients were compared (10.3% versus 14.3%, respectively; P=0.16).

**Cardiovascular Medication Use**

There were no significant differences between study groups in cardiovascular medication use during the Holter recordings at either baseline or 1 year (Table 3). Thienopyridine use was significantly more common in the PCI group at baseline (92%) versus 14.3%, respectively; P<0.16).

**Primary End Point**

There was no significant difference between the medical therapy and PCI groups in the change in α1 (medical therapy

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### Table 1. Baseline Clinical Characteristics for OAT-EP and Other OAT Patients

<table>
<thead>
<tr>
<th></th>
<th>OAT-EP PCI Group (n=149)</th>
<th>OAT-EP Medical Therapy Group (n=151)</th>
<th>OAT-EP Both Groups (n=300)</th>
<th>Other OAT Patients (n=1901)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, y</td>
<td>57.2±10.5</td>
<td>57.6±10.5</td>
<td>57.4±10.5</td>
<td>58.8±11.0</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>111 (74.5)</td>
<td>127 (84.1)</td>
<td>238 (79.3)</td>
<td>1479 (77.8)</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>115 (77.2)</td>
<td>117 (77.5)</td>
<td>232 (77.3)</td>
<td>1531 (80.5)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (2.0)</td>
<td>4 (2.6)</td>
<td>7 (2.3)</td>
<td>62 (3.3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>26 (17.4)</td>
<td>21 (13.9)</td>
<td>47 (15.7)</td>
<td>230 (12.1)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (3.4)</td>
<td>9 (6.0)</td>
<td>14 (4.7)</td>
<td>78 (4.1)</td>
</tr>
<tr>
<td>History of, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>28 (18.8)</td>
<td>30 (19.9)</td>
<td>58 (19.3)</td>
<td>437 (23.0)</td>
</tr>
<tr>
<td>Prior MI</td>
<td>10 (6.7)</td>
<td>10 (6.6)</td>
<td>20 (6.7)</td>
<td>227 (11.9)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>4 (2.7)</td>
<td>6 (4.0)</td>
<td>10 (3.3)</td>
<td>72 (3.8)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>5 (3.4)</td>
<td>6 (4.0)</td>
<td>11 (3.7)</td>
<td>72 (3.8)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>5 (3.4)</td>
<td>3 (2.0)</td>
<td>8 (2.7)</td>
<td>44 (2.3)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>5 (3.4)</td>
<td>10 (6.6)</td>
<td>15 (5.0)</td>
<td>90 (4.7)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22 (14.8)</td>
<td>40 (26.5)</td>
<td>62 (20.7)</td>
<td>392 (20.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>81 (54.4)</td>
<td>94 (62.3)</td>
<td>175 (58.3)</td>
<td>896 (47.1)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>55 (36.9)</td>
<td>64 (42.4)</td>
<td>119 (39.7)</td>
<td>740 (38.9)</td>
</tr>
<tr>
<td>NYHA class at randomization, n (%)</td>
<td>126 (84.6)</td>
<td>122 (80.8)</td>
<td>248 (82.7)</td>
<td>1582 (83.4)</td>
</tr>
<tr>
<td>I</td>
<td>23 (15.4)</td>
<td>29 (19.2)</td>
<td>52 (17.3)</td>
<td>315 (16.6)</td>
</tr>
<tr>
<td>II</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Glomerular filtration rate, mean±SD, ml/min</td>
<td>83.5±23.6</td>
<td>83.5±23.5</td>
<td>83.5±23.5</td>
<td>80.2±21.2</td>
</tr>
</tbody>
</table>
change minus PCI change, −0.04; 95% CI, −0.12 to 0.04; Table 4 and Figure 2A). On multivariable analysis of the change in α1, the treatment group assignment (PCI versus medical therapy) was still not a significant predictor (P=0.31) after adjustment for baseline clinical variables and cardiovascular medication use during the Holter recordings. There was no significant change in α1 at 1 year compared with baseline within the medical therapy or PCI group (Table 4 and Figure 2A).

Table 2. Index MI and Angiographic Characteristics for OAT-EP and Other OAT Patients

<table>
<thead>
<tr>
<th></th>
<th>OAT-EP PCI Group (n=149)</th>
<th>OAT-EP Medical Therapy Group (n=151)</th>
<th>OAT-EP Both Groups (n=300)</th>
<th>Other OAT Patients (n=1901)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-segment elevation, new Q waves, or loss of R waves, n (%)</td>
<td>132 (88.6)</td>
<td>135 (89.4)</td>
<td>267 (89.0)</td>
<td>1638 (86.2)</td>
</tr>
<tr>
<td>Thrombolytic therapy within first 24 h of index MI, n (%)</td>
<td>20 (13.4)</td>
<td>22 (14.6)</td>
<td>42 (14.0)</td>
<td>382 (20.1)</td>
</tr>
<tr>
<td>Interval from MI to randomization, median (25th–75th percentile), d</td>
<td>12 (6–21)</td>
<td>11 (6–20)</td>
<td>12 (6–21)</td>
<td>8 (5–15)</td>
</tr>
<tr>
<td>Stress test performed, n (%)</td>
<td>42 (28.2)</td>
<td>39 (25.8)</td>
<td>81 (27.0)</td>
<td>517 (27.2)</td>
</tr>
<tr>
<td>Ischemia in IRA territory, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (4.8)</td>
<td>1 (2.6)</td>
<td>3 (3.7)</td>
<td>56 (10.8)</td>
</tr>
<tr>
<td>Mild</td>
<td>10 (25.6)</td>
<td>9 (24.0)</td>
<td>23 (28.4)</td>
<td>157 (30.4)</td>
</tr>
<tr>
<td>None</td>
<td>27 (64.3)</td>
<td>28 (71.8)</td>
<td>55 (67.9)</td>
<td>303 (68.6)</td>
</tr>
<tr>
<td>IRA, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>52 (34.9)</td>
<td>51 (33.8)</td>
<td>103 (34.3)</td>
<td>690 (36.3)</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>19 (12.8)</td>
<td>23 (15.2)</td>
<td>42 (14.0)</td>
<td>293 (15.4)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>78 (52.3)</td>
<td>77 (51.0)</td>
<td>155 (51.7)</td>
<td>918 (48.3)</td>
</tr>
<tr>
<td>IRA TIMI flow grade, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>112 (75.2)</td>
<td>120 (79.5)</td>
<td>232 (77.3)</td>
<td>1573 (83.7)</td>
</tr>
<tr>
<td>1</td>
<td>37 (24.8)</td>
<td>31 (20.5)</td>
<td>68 (22.7)</td>
<td>298 (15.8)</td>
</tr>
<tr>
<td>2</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td>3</td>
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<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Collateral vessels present, n (%)</td>
<td>131 (87.9)</td>
<td>132 (87.4)</td>
<td>263 (87.7)</td>
<td>1659 (88.6)</td>
</tr>
<tr>
<td>Multivessel disease, n (%)</td>
<td>27 (18.1)</td>
<td>43 (28.5)</td>
<td>70 (23.3)</td>
<td>309 (16.4)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, mean±SD</td>
<td>47.7±10.9</td>
<td>47.9±10.3</td>
<td>47.8±10.6</td>
<td>47.7±11.2</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;50%, n (%)</td>
<td>79 (53.0)</td>
<td>74 (49.0)</td>
<td>153 (51.0)</td>
<td>1017 (54.0)</td>
</tr>
</tbody>
</table>

TIMI indicates Thrombolysis in Myocardial Infarction.

Secondary End Points

There were no significant differences between the medical therapy and PCI groups in the changes in fQRS or TWV (medical therapy change minus PCI change; fQRS, 2.2 ms; 95% CI, −1.4 to 5.9 ms; TWV, 3.0 μV; 95% CI, −4.8 to 10.7 μV; Table 4 and Figures 2B and 2C). Separate multivariable models were constructed for the change in fQRS and the change in TWV. Treatment group assignment was still not a significant predictor (P=0.14 for fQRS and P=0.89 for

Table 3. Medical Therapy During Holter Recording

<table>
<thead>
<tr>
<th></th>
<th>Baseline PCI (n=149), n (%)</th>
<th>Baseline Medical Therapy (n=149), n (%)</th>
<th>1 Year PCI (n=131), n (%)</th>
<th>1 Year Medical Therapy (n=138), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>120 (80.5)</td>
<td>121 (81.2)</td>
<td>97 (74.0)</td>
<td>109 (79.0)</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>5 (3.4)</td>
<td>3 (2.0)</td>
<td>9 (6.9)</td>
<td>10 (7.2)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>133 (89.3)</td>
<td>138 (92.6)</td>
<td>116 (88.5)</td>
<td>128 (92.8)</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>8 (5.4)</td>
<td>11 (7.4)</td>
<td>7 (5.3)</td>
<td>15 (10.9)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>1 (0.7)</td>
<td>3 (2.0)</td>
<td>0 (0.0)</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>24 (16.1)</td>
<td>30 (20.1)</td>
<td>25 (19.1)</td>
<td>35 (25.4)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>6 (4.0)</td>
<td>10 (6.7)</td>
<td>8 (6.1)</td>
<td>10 (7.2)</td>
</tr>
<tr>
<td>Class I or III antiarrhythmic</td>
<td>2 (1.3)</td>
<td>4 (2.7)</td>
<td>4 (3.1)</td>
<td>2 (1.4)</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme.
TWV) in either model after adjustment for baseline clinical variables and cardiovascular medication use during the Holter recordings.

There was a small but significant increase in fQRS within the medical therapy group (Table 4 and Figure 2B). No significant changes in fQRS were observed within the PCI group. There was a small but significant decrease in TWV in the overall study group and within the PCI group (Table 4 and Figure 2B). No significant changes in TWV were observed in the medical therapy group (Table 4 and Figure 2B). No significant changes in TWV were observed within the PCI group.

**Secondary Analyses**

The analysis of all available data at 1 year revealed no significant differences in α1, fQRS, or TWV (α1: 1.07 versus 1.02, P = 0.19; fQRS: 113.1 versus 114.3 ms, P = 0.55; TWV: 36.4 versus 36.9 μV, P = 0.84, for the PCI and medical therapy groups, respectively). Four patients in the PCI group and 1 patient in the medical therapy group had recurrent MI before the 1-year Holter measurements were performed. A sensitivity analysis revealed that excluding patients with recurrent MI did not alter the primary study results (changes from baseline to 1 year in α1: 0.00 versus −0.03, P = 0.45; fQRS: 1.6 versus 3.7 ms, P = 0.26; TWV: −6.7 versus −3.4 μV, P = 0.40, for the PCI and medical therapy groups, respectively). The primary study results were unchanged when the data were analyzed after exclusion of crossovers within 30 days (as-treated analysis; changes from baseline to 1 year in α1: 0.00 versus −0.04, P = 0.35; fQRS: 2.0 versus 3.8 ms, P = 0.35; TWV: −7.0 versus −2.7 μV, P = 0.29, for the PCI and medical therapy groups, respectively). There were no significant differences between the PCI and medical therapy groups in the changes in primary and major secondary end points at 30 days (α1: −0.03 versus −0.05, P = 0.63; fQRS: −1.4 versus 0.6 ms, P = 0.17; TWV: −1.7 versus −1.0 μV, P = 0.88, for the PCI and medical therapy groups, respectively).

There were significant increases between baseline and 1 year in several time-domain and frequency-domain HRV variables (mean RR interval, SD of normal-to-normal interval; SDANN, SD of average normal-to-normal intervals calculated over 5 minutes; pNN50, proportion of successful intervals that differ by more than 50 ms; rMSSD, root mean square of successive differences; VLF, very low frequency; LF, low frequency; and HF, high frequency. There were no significant differences between the PCI and medical therapy groups in the changes of any of the listed variables (P > 0.2 for all comparisons).

**Table 4. Changes in Arrhythmia Marker Values Between Baseline and 1 Year**

<table>
<thead>
<tr>
<th></th>
<th>PCI Group</th>
<th></th>
<th>Medical Therapy Group</th>
<th></th>
<th>Medical Therapy Change–PCI Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Baseline</td>
<td>1 Year</td>
<td>Change</td>
<td>n</td>
</tr>
<tr>
<td>α1</td>
<td>118</td>
<td>1.05±0.30</td>
<td>1.06±0.27</td>
<td>0.01±0.34</td>
<td>119</td>
</tr>
<tr>
<td>TWV, μV</td>
<td>104</td>
<td>44.0±28.4</td>
<td>37.7±21.5*</td>
<td>−6.3±25.1</td>
<td>103</td>
</tr>
<tr>
<td>Time-domain SAECG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fQRS, ms</td>
<td>90</td>
<td>110.4±12.4</td>
<td>111.9±13.2</td>
<td>1.5±12.4</td>
<td>81</td>
</tr>
<tr>
<td>LAS, ms</td>
<td>94</td>
<td>36.5±11.6</td>
<td>34.2±11.9</td>
<td>−2.2±11.6</td>
<td>84</td>
</tr>
<tr>
<td>RM540, μV</td>
<td>95</td>
<td>27.3±18.1</td>
<td>30.4±21.3</td>
<td>3.1±19.4</td>
<td>84</td>
</tr>
<tr>
<td>Time-domain HRV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean RR interval, ms</td>
<td>128</td>
<td>927.9±162.1</td>
<td>980.1±150.9*</td>
<td>52.2±191.1</td>
<td>122</td>
</tr>
<tr>
<td>SDNN, ms</td>
<td>128</td>
<td>31.5±14.8</td>
<td>38.9±16.4*</td>
<td>7.5±18.1</td>
<td>122</td>
</tr>
<tr>
<td>SDANN, ms</td>
<td>119</td>
<td>7.5±6.1</td>
<td>9.1±6.9</td>
<td>1.6±6.8</td>
<td>109</td>
</tr>
<tr>
<td>rMSSD, ms</td>
<td>128</td>
<td>21.2±11.9</td>
<td>27.2±14.7*</td>
<td>5.9±15.7</td>
<td>122</td>
</tr>
<tr>
<td>pNN50, %</td>
<td>75</td>
<td>6.5±8.9</td>
<td>9.3±10.5</td>
<td>2.8±11.5</td>
<td>78</td>
</tr>
<tr>
<td>Frequency-domain HRV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total power</td>
<td>95</td>
<td>689.5±685.6</td>
<td>947.3±625.8*</td>
<td>257.8±897.6</td>
<td>81</td>
</tr>
<tr>
<td>VLF</td>
<td>95</td>
<td>282.5±223.4</td>
<td>338.2±250.2</td>
<td>55.7±347.2</td>
<td>81</td>
</tr>
<tr>
<td>LF</td>
<td>95</td>
<td>213.3±240.2</td>
<td>297.3±303.8</td>
<td>83.9±346.6</td>
<td>81</td>
</tr>
<tr>
<td>HF</td>
<td>95</td>
<td>111.5±140.7</td>
<td>166.4±175.0*</td>
<td>54.9±175.3</td>
<td>81</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>95</td>
<td>3.4±3.1</td>
<td>2.7±2.2</td>
<td>−0.7±3.3</td>
<td>81</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD. LAS indicates low-amplitude signal; RMS, root mean square; SDNN, SD of normal-to-normal interval; SDANN, SD of average normal-to-normal intervals calculated over 5 minutes; pNN50, proportion of successful intervals that differ by more than 50 ms; rMSSD, root mean square of successive differences; VLF, very low frequency; LF, low frequency; and HF, high frequency. There were no significant differences between the PCI and medical therapy groups in the changes of any of the listed variables (P > 0.2 for all comparisons).

*P < 0.01 for the change between baseline and 1 year within the group indicated.

**Discussion**

The major findings of this study are that PCI with stenting of a persistently occluded IRA during the subacute phase after MI compared with medical therapy alone had no significant effect on changes in HRV, the time-domain SAECG, or TWV during the first year after MI. Although late IRA patency was achieved in 83% of OAT patients and at least moderately
retained viability was present at baseline in 69%. PCI had no significant effect on changes in the major determinants of arrhythmia vulnerability: the autonomic nervous system (HRV), impulse conduction (SAECG), and ventricular repolarization (TWV).

Several mechanisms have been proposed to explain the presumed benefits of late opening of the IRA, including prevention of ventricular remodeling, improvement of left ventricular function by recovery of hibernating myocardium, and stabilization of the electrophysiological substrate. In an animal model of experimental MI, late reperfusion reduced the incidence of arrhythmic death compared with permanent coronary artery occlusion despite identical infarct size in the 2 groups. However, clinical studies that examined the effects of balloon angioplasty without adjunctive stenting on arrhythmia markers have yielded conflicting results. These studies were limited by small sample sizes, lack of treatment randomization, the use of patients with failed angioplasty as controls, and likely poor long-term vessel patency because stents were not used.

The present study is the first large, adequately powered, randomized controlled trial to investigate whether PCI with stenting of occluded coronary arteries late after MI reduces markers of vulnerability to ventricular arrhythmias. We did not observe any significant effect of PCI on changes in HRV (α1), myocardial impulse conduction (fQRS), or ventricular repolarization (TWV) at 1 year. There was a significant increase in fQRS within the medical therapy group and a significant decrease in TWV within the PCI group. Although these within-group changes could be interpreted as a small benefit of PCI (improvement in TWV within the PCI group, worsening of fQRS within the medical therapy group), these changes were not significantly different when the treatment groups (PCI versus medical therapy) were compared. Furthermore, the magnitude of these changes was far below the differences that we prespecified as clinically relevant to detect on the basis of prior outcome data when we calculated the required sample size for the study (10-ms change in fQRS, 10-μV change in TWV). The results of OAT-EP are concordant with the results of OAT, which did not suggest an effect of PCI on total mortality, cardiac death, death from arrhythmia, sudden unexplained death, or development of sustained ventricular tachycardia or need for implantable cardioverter-defibrillator placement.

It is well recognized that traditional time- and frequency-domain HRV variables change to a greater extent than α1 after MI. We observed an identical pattern in our study; α1 was unchanged, but several time- and frequency-domain HRV variables increased substantially between baseline and 1 year. Importantly, there were no significant differences between the PCI and medical therapy groups in the changes in any of the study variables. Because we did observe improvement in most HRV variables and changes in fQRS and TWV, these data indicate that our study variables were sensitive enough to detect changes in critical electrophysiological characteristics and that PCI had no effect on these variables. Furthermore, because prior studies indicate that HRV is maximally recovered by 1 year after MI, it is
unlikely that more extended follow-up would have changed our results.

Study Limitations
Because many OAT-EP centers performed the OAT treatment randomization (PCI versus medical therapy) immediately after the qualifying angiogram, all baseline electrophysiological measures had to be acquired before the angiogram. Long-term Holter recordings and exercise T-wave alternans assessment were not feasible because these additional requirements would have delayed the qualifying angiogram and limited enrollment and because most centers did not have T-wave alternans equipment. Although HRV increases with the length of the recording (10 minutes versus 24 hours), the results of short-term recordings correlate well with 24-hour recordings and are suitable for measuring changes over time. Furthermore, the prognostic value of short-term Holter recordings has been demonstrated for traditional HRV parameters and for α1.15,23,24 There is less experience with TWV than T-wave alternans, and the precise relation between the 2 techniques requires further study. However, because TWV was previously demonstrated to have prognostic value in high-risk patients with coronary artery disease in the landmark Multicenter Automatic Defibrillator Implantation Trial II trial, it should provide an accurate assessment of ventricular repolarization in OAT-EP patients.

The use of follow-up Holter recordings is subject to bias because of deaths within the first year and difficulty in obtaining follow-up on sicker patients. However, we did not observe any important differences in the baseline clinical characteristics of patients with and without 1-year data available, which suggests that sicker patients were not excluded. Furthermore, the numbers of patients in the PCI and medical therapy groups who did not have complete data at baseline and 1 year because of death and other reasons were similar.

Although it is possible that OAT-EP patients are not fully representative of patients in the community who meet OAT eligibility criteria, we view this as unlikely given that OAT-EP patients were comparable to patients in the main OAT trial, the OAT pretrial registry, and the concurrent OAT registry with respect to most important baseline clinical characteristics. Importantly, long-term outcomes were similar in OAT-EP and other patients in the main OAT trial, suggesting that lower-risk patients were not inadvertently selected to participate in OAT-EP.

Conclusions
PCI with stenting of a persistently occluded IRA during the subacute phase after MI compared with medical therapy alone had no significant effect on changes in HRV, the time-domain SAECG, or TWV during the first year after MI. Given the absence of clinical benefit in OAT, routine PCI is not recommended for persistent IRA occlusion in stable patients during the subacute phase after MI.

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**CLINICAL PERSPECTIVE**

The late open artery hypothesis posits that clinical outcomes can be improved by late opening of persistently occluded infarct-related arteries during the subacute phase of myocardial infarction, when myocardial salvage is not anticipated. Several mechanisms have been proposed for the putative benefit of late reperfusion, including stabilization of the electrophysiological substrate and downstream prevention of malignant ventricular arrhythmias. This ancillary study of the Occluded Artery Trial evaluated the effects of late opening and stenting of an occluded infarct artery on several noninvasive measures of electrophysiological stability during the first year after myocardial infarction. Heart rate variability, assessing the autonomic nervous system, was the primary measure. Major secondary measures evaluated repolarization (dynamic changes in T-wave morphology [T-wave variability]) and delayed myocardial conduction (filtered QRS duration on the signal-averaged ECG). Compared with medical therapy alone, late reperfusion and stenting of a persistently occluded infarct-related artery did not change heart rate variability, filtered QRS, or T-wave variability during the first year after myocardial infarction. These results are consistent with the lack of clinical benefit, including no reduction in sudden death, with PCI for stable patients with persistently occluded infarct-related arteries after myocardial infarction in the main Occluded Artery Trial.
Electrophysiological Effects of Late Percutaneous Coronary Intervention for Infarct-Related Coronary Artery Occlusion: The Occluded Artery Trial-Electrophysiological Mechanisms (OAT-EP)
Eric J. Rashba, Gervasio A. Lamas, Jean-Philippe Couderc, Sharri M. Hollist, Vladimir Dzavik, Witold Ruzylo, Viliam Fridrich, Christopher E. Buller, Sandra A. Forman, Joseph A. Kufera, Antonio C. Carvalho and Judith S. Hochman
for the OAT-EP Investigators

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